REMARKS

Applicant requests reconsideration of the application in view of the discussion that follows. The status of the claims as of this response is as follows: Claims 1-32 are pending. Claims 10-32 were withdrawn from consideration and have been canceled herein. Applicant reserves the right to file one or more divisional applications to the separately patentable subject matter of claims 10-32. Claims 1, 2, 4 and 5 have been amended herein and claims 33-38 have been added.

The Amendment

Claim 1 was amended to refer to degenerate biopolymers comprising nucleotides. Support therefor is in the specification, for example, page 9, lines 9-19.

Claim 2 was amended to satisfy its dependency from claim 1.

Claim 4 was amended in a manner similar to that for claim 1 above.

Claim 5 was amended to satisfy its dependency from claim 4.

Claim 33 has been added and finds support in the specification, for example, original claim 4, page 25, lines 13-16, and page 26, lines 21-22.

Claims 34-38 have been added and find support in the specification, for example, original claims 5-9.

Restriction Requirement

The Office Action asserts that arguments made by Applicant regarding the restriction requirement were fundamentally flawed. Applicant disagrees. In making the restriction requirement, the Office Action is acknowledging at least implicitly that the inventions of the aforementioned groups are separately patentable over one other. If this were not the case, then the restriction requirement would not be proper. Furthermore, it follows from the above that art (if such art exists) that discloses no more than the subject matter of the claims of one of the above groups cannot render known or obvious the invention of the other groups. If this were not the case, then the restriction requirement with respect to those claims would not be proper. Applicant submits that, to the extent that the Office Action is asserting a contrary position, the restriction requirement would be improper.

Applicant recognizes that the M.P.E.P. does state, "though they may each be unpatentable because of the prior art." However, this language must only mean that there may be art that renders one of the inventions unpatentable and other art that

renders another of the inventions unpatentable. The language cannot mean that art disclosing no more than the subject matter of the claims of one of the groups and anticipating or rendering obvious the invention of that group would also anticipate or render obvious the inventions of the other group. If so, then the inventions of the separate groups would not be patentable over one another and the restriction requirement would be improper.

The assertions in the Office Action are directed to hypothetical situations other than that set forth by Applicant. In any event the Office Action has explicitly stated on the record that the groups set forth in the restriction requirement are separately patentable over each other.

Information Disclosure Statement

The Office Action contends that the Information Disclosure Statement (original IDS) filed by Applicant contains certain citations to U.S. patents that have incorrect citation of the patent numbers. First, the citations referred to in the original IDS are listed under the category of U.S. Patent Documents, which includes both U.S. patents and U.S. patent application publications. Applicant submits that the original IDS provided sufficient information to identify these patent application publications since the original IDS included both a date and a document number for each document. For example, the original IDS listed 0,124,588 dated Jul. 3, 2003. This citation translates into 20030124588 where the year identifier appears prior to the document number. In order to advance the prosecution of the present application, Applicant is providing herewith a supplemental IDS where each U.S. patent application publication cited in the original IDS is repeated in the supplemental IDS.

Drawings

Applicant acknowledges the indication in the Office Action that the drawings received on November 25, 2003, are acceptable.

Rejections under 35 U.S.C. §112

Claims 1-9 were rejected under the first paragraph of the above code section. The Office Action contends that, because the specification, while being enabling for a method of synthesizing a plurality of biopolymers at a predetermined locations of a surface of a substrate, wherein one or more of the feature locations comprises

degenerate biopolymers, wherein the biopolymers are nucleic acid (i.e., polynucleotide, oligonucleotide), does not reasonably provide enablement for the method wherein the degenerate biopolymers are polypeptides. The specification, continues the Office Action, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Without acquiescing in the contentions in the Office Action, Applicant submits that the amendments to the claims obviate this ground of rejection.

Rejections under 35 U.S.C. §102

Claims 1-7 and 9 were rejected under 35 U.S.C. 102(e) as being anticipated by Cronin, *et al.* (U.S. Patent No. 6,027,880) (Cronin).

The Office Action argues that Cronin discloses a method of synthesizing a cystic fibrosis mutation chip, which comprises a plurality of oligonucleotides immobilized at predetermined locations. The Office Action further asserts that the array comprises a reference sequence tiled thereto followed by the tiling of the subgroups of oligonucleotides, which comprise the same sequence as that of the reference oligonucleotide sequence excepting that the subgroups of oligonucleotides comprise at least one nucleotide that is different from the reference sequence (referring to Cronin at Figures 1 and 5; column 2, lines 43-49; column 3, lines 36-40; column 11, lines 24-28, 33-35, and 42-46). The Office Action also contends that Cronin discloses that the array is fabricated via photolithography, which comprises the steps of providing nucleotide monomers onto an array substrate where the monomers are blocked at their 5'-OH ends with a photoremovable blocking group. The above step, continues the Office Action, is followed by deprotection via mask-mediated photolithography (thus activation). The Office Action further contends that the processes are repeated subsequent to the deprotection steps, so as to fabricate the array (referring to column 52, lines 13-28, of Cronin). Claims 1-7, concludes the Office Action, are thereby clearly anticipated.

Claim 1 of the present application is directed to a method for synthesizing a plurality of biopolymers comprising nucleotides at predetermined feature locations on a surface of a substrate wherein one or more of said feature locations comprises degenerate biopolymers comprising nucleotides. The method comprises, in each round of multiple rounds of subunit additions, providing one or more biopolymer

subunit precursors comprising nucleotides at each of multiple feature locations on the surface to form the plurality of biopolymers on the surface. For one or more feature locations comprising the degenerate biopolymers, the biopolymer subunit precursors comprise a mixture of biopolymer subunit precursors for forming the degenerate biopolymers at the feature location.

An invention is anticipated if each and every limitation of the claimed invention is disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994). It is not enough, however, that the prior art reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention arranged in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 U.S.P.Q. 481, 485 (Fed. Cir. 1984). In addition, the allegedly anticipating reference must be enabling and describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art. *In re Paulsen*, *supra*, at 1673. The anticipation determination is viewed from one of ordinary skill in the art. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

Cronin fails to disclose or suggest at least the following elements of claim 1. First, the reference does not disclose or suggest a substrate on the surface of which a plurality of biopolymers comprising nucleotides are synthesized at predetermined feature locations wherein one or more of said feature locations comprises degenerate biopolymers comprising nucleotides. This is clear from the discussion in the reference, for example, at col. 3, lines 38-43, where the patentee states that each of the variants is assigned a designation and an array of pooled probes is provided with each pool occupying a separate cell of the array. The patentee further states that each pool comprises a probe comprising a segment exactly complementary to each variant sequence assigned a particular designation.

Second, Cronin fails to disclose or suggest a method of synthesis wherein a mixture of biopolymer subunit precursors is employed at a feature site to form the feature location comprising the degenerate biopolymers. The Cronin reference does not disclose such a feature. As a matter of fact, as recognized in the Office Action,

the Cronin method employs photolithography where masks are employed. The patentee refers to depositing a nucleoside building block, itself protected with a protecting group to the activated area of the support. See, for example, col. 52, lines 13-28, and Fig. 22. As is known in the art, such technology typically involves generally applying the nucleoside building block to the surface of the substrate where the mask protects the feature areas that are not to react with the nucleoside building block. Cronin discloses no more than the known technology of depositing a single nucleotide precursor at each feature location. Furthermore, since the reference does not disclose or suggest a surface of a support comprising a plurality of biopolymers comprising nucleotides synthesized at predetermined feature locations wherein one or more of said feature locations comprises degenerate biopolymers comprising nucleotides, then it follows that there would be no disclosure or suggestion of using mixtures of biopolymer subunit precursors to add to a feature location and one skilled in the art would not expect to find such a disclosure or suggestion in Cronin.

Claims 2 and 3 each depend from claim 1 and are, therefore, patentable over Cronin by virtue of such dependency since claim 1 is patentable over Cronin as demonstrated above.

Independent claim 4 is patentable over Cronin for reasons similar to those discussed above with regard to the rejection of claim 1 over Cronin. The reference fails to disclose or suggest at least the following elements of claim 4: (i) a substrate on the surface of which a plurality of biopolymers comprising nucleotides are synthesized at predetermined feature locations wherein one or more of said feature locations comprises degenerate biopolymers comprising nucleotides and (ii) a method of synthesis wherein a mixture of biopolymer subunit precursors is deposited at a feature site to form the feature location comprising the degenerate biopolymers.

Claims 5-7 and 9 each depend ultimately from claim 4 and are, therefore, patentable over Cronin by virtue of such dependency since claim 4 is patentable over Cronin as demonstrated above.

New claims 33-38 are patentable over Cronin for reasons similar to those discussed above with respect to claims 1-9. Furthermore, Cronin does not disclose or suggest the limitations of claim 33 wherein a mixture comprising a predetermined ratio of the biopolymer subunit precursors for forming the degenerate biopolymers is dispensed in a droplet manner at the feature locations.

Rejections under 35 U.S.C. §103

Claim 8 was rejected under 35 U.S.C. §103(a) as being unpatentable over Cronin in view of Baldeschwieler, *et al.* (WO 95/25116) (Baldeschwieler). The Office Action recognizes that Cronin does not explicitly disclose a method of synthesizing an array involving a dispenser comprising at least one droplet dispensing device. However, asserts the Office Action, Baldeschwieler discloses a method of synthesizing an array via use of an inkjet technology, wherein the method involves the attachment of molecules onto a substrate surface, for sequential synthesis of polynucleotides, wherein the reagents are dispensed from a microdrop dispensing device. The Office Action concludes that it would have been *prima facie* obvious to one skilled in the art to combine the teachings of Cronin with that of Baldeschwieler.

Without acquiescing in the arguments in the Office Action, Applicant submits that claim 8 depends ultimately from claim 4, which is patentable over Cronin because Cronin is deficient in not disclosing each and every element of claim 4. Claim 8 is, therefore, patentable over a combination of the teachings of Cronin and Baldeschwieler by virtue of such dependency. Furthermore, Baldeschwieler does not cure the deficiencies of the Cronin reference.

Claims 1-9 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hanks, *et al.* (Methods in Enzymology, 1991, vol. 200, pages 525-532) (Hanks) in view of Baldeschwieler.

In order to maintain a rejection under 35 U.S.C. §103 the Examiner must first establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification. *In re Lintner*, 458 F.2d 1013, 173 U.S.P.Q. 560 (C.C.P.A. 1972). In asserting a *prima facie* case of obviousness involving more than one reference, the Examiner must show some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references offered by the Examiner as evidence of obviousness. *In re Lalu*, 747 F.2d 703; 223 U.S.P.Q. 1257 (Fed. Cir. 1984). In determining the scope and content of the prior art, references must be

considered in their entirety, as a whole, including portions that would lead away from the claimed invention. *In re Panduit*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed Cir. 1987). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine*, *supra*.

Hanks discusses the use of degenerate oligonucleotide probes to identify clones that encode protein kinases. A mixture of degenerate probes, which are labeled, is employed as hybridization probes and the mixture is present in a hybridization solution. The author describes using standard procedures to plate a cDNA library, transfer colonies or phage onto nitrocellulose or nylon filters and liberating and binding DNA to the filters. The mixture of labeled degenerate probes is added to a bag containing the filter with the bound DNA and hybridization is allowed to occur. The resulting filter is washed and examined for the presence of the label.

Hanks is completely devoid of any teaching relevant to the presently claimed inventions. For example, Hanks fails to disclose or suggest a method for synthesizing a plurality of biopolymers comprising nucleotides at predetermined feature locations on a surface of a substrate wherein one or more of said feature locations comprises degenerate biopolymers comprising nucleotides. Hanks refers only to putting cDNA libraries for novel protein kinases onto filter materials. The reference does not disclose or suggest using multiple rounds of subunit additions in which one or more biopolymer subunit precursors comprising nucleotides are placed at each of multiple feature locations on the surface to form the plurality of biopolymers on the surface. Furthermore, Hanks fails to disclose or suggest either that one or more feature locations comprise degenerate biopolymers or that the biopolymer subunit precursors comprise a mixture of biopolymer subunit precursors for forming the degenerate biopolymers at the feature location.

The Office Action appears to recognize the deficiencies of Hanks. However, the Office Action asserts that the teaching of Baldeschwieler combined with that of Hanks cures all of the deficiencies of Hanks and that one skilled in the art would be motivated to combine the teachings of the references to arrive at the presently claimed invention for the well known benefit of simultaneously identifying a plurality of homologous genes of interest.

Applicant submits that one skilled in the art would not be able to arrive at the presently claimed invention based on the teachings of the references without using

Applicant's own disclosure. Even if the skilled artisan would be inclined to combine the teachings of the references, there would be no reason, absent the teaching of Applicant, to prepare a surface of a substrate having a plurality of biopolymers comprising nucleotides at predetermined feature locations on a surface of a substrate wherein one or more of the feature locations comprises degenerate biopolymers comprising nucleotides. Although Hanks uses a hybridization solution comprising degenerate oligonucleotides, virtually all of the codon possibilities for a conserved stretch may be included in the mixture (Hanks, page 525). How does this disclosure, absent Applicant's teaching, translate into a surface with one or more feature locations comprising degenerate biopolymers? Even if the skilled artisan would be inclined to combine the teachings of the references, there would be no reason, absent the teaching of Applicant, to utilize a mixture of biopolymer subunit precursors for forming the degenerate biopolymers at the feature locations as set forth in Applicant's claims.

The Office Action asserts that it would be obvious to fabricate a microarray comprising a plurality of degenerate oligonucleotide probes for the well known benefit of simultaneously identifying a plurality of homologous genes of interest. Even if for the sake of argument one were to accept this assertion as true, one is still not in possession of Applicant's claimed invention. At most, the skilled artisan might be inclined to deposit each degenerate oligonucleotide or precursor to a different feature location on the surface of a substrate. Why, absent Applicant's own teaching, would one skilled in the art deposit mixtures of degenerate oligonucleotides or precursors thereof at a single feature location?

The Office Action attempts to address this issue by contending that, given the fact that Hanks gave all the necessary guidance for generating degenerate oligonucleotide probes for identifying related genes, which, coupled with the teachings of Baldeschwieler, who gave all the necessary guidance for fabricating an array via use of a dispenser, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success at combining the teachings so as to arrive at the method of fabricating, on a solid substrate, a plurality of degenerate oligonucleotide probes.

The problem with the above contention is that, even if for the sake of argument one would accept it as true, the method arrived at (method of fabricating on a solid substrate a plurality of degenerate oligonucleotide probes) is not that

presently claimed. Applicant's claims are directed to a method of synthesizing a plurality of biopolymers comprising nucleotides on the surface of a substrate wherein one or more feature locations comprise degenerate biopolymers and wherein the biopolymer subunit precursors that are applied to a feature location comprise a mixture of biopolymer subunit precursors for forming the degenerate biopolymers at the feature location.

Claims 2 and 3 each depend from claim 1 and are, therefore, patentable over the combined teachings of Hanks and Baldeschwieler by virtue of such dependency since claim 1 is patentable over the combined teachings of Hanks and Baldeschwieler as demonstrated above.

Independent claim 4 is patentable over the combined teachings of Hanks and Baldeschwieler for reasons similar to those discussed above with regard to the rejection of claim 1 over the combined teachings of Hanks and Baldeschwieler. Even if for the sake of argument one were motivated to combine the teachings of the references, the combination of teachings fails to disclose or suggest at least the following elements of claim 4: (i) a substrate on the surface of which a plurality of biopolymers comprising nucleotides is synthesized at predetermined feature locations wherein one or more of the feature locations comprises degenerate biopolymers comprising nucleotides and (ii) a method of synthesis wherein a mixture of biopolymer subunit precursors is deposited at a feature site to form a feature location comprising the degenerate biopolymers.

Claims 5-9 each depend ultimately from claim 4 and are, therefore, patentable over the combined teachings of Hanks and Baldeschwieler by virtue of such dependency since claim 4 is patentable over the combined teachings of Hanks and Baldeschwieler as demonstrated above.

New claims 33-38 are patentable over Hanks and Baldeschwieler for reasons similar to those discussed above with respect to claims 1-9. Furthermore, the combination of the teaching of Hanks and Baldeschwieler does not disclose or suggest the limitations of claim 33 wherein a mixture comprising a predetermined ratio of the biopolymer subunit precursors for forming the degenerate biopolymers is dispensed in a droplet manner at each of the feature locations.

Conclusion

Claims 1-9 and 33-38 satisfy the requirements of 35 U.S.C. §§112, 102 and 103. Allowance of the above-identified patent application, it is submitted, is in order.

Respectfully submitted,

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